RAAS BLOCKADE BETWEEN OPTIMIZATION AND ABUSE

AHMED ELKERAIE

PICO QUESTIONS

- *Is the use of ACEIs/ARBs as compared to other classes better in incident hypertensive patient?*
- *Is the use of ACEIs/ARBs as compared to other classes better in diabetic non hypertensive non proteinuric patient?*
- *Is the use of ACEIs/ARBs as compared to other classes better in diabetic hypertensive non proteinuric patient?*
- *Is the use of ACEIs/ARBs as compared to other classes better in diabetic hypertensive proteinuric A2 patient?*
- *Is the use of ACEIs/ARBs as compared to other classes better in diabetic hypertensive proteinuric A3 patient?*

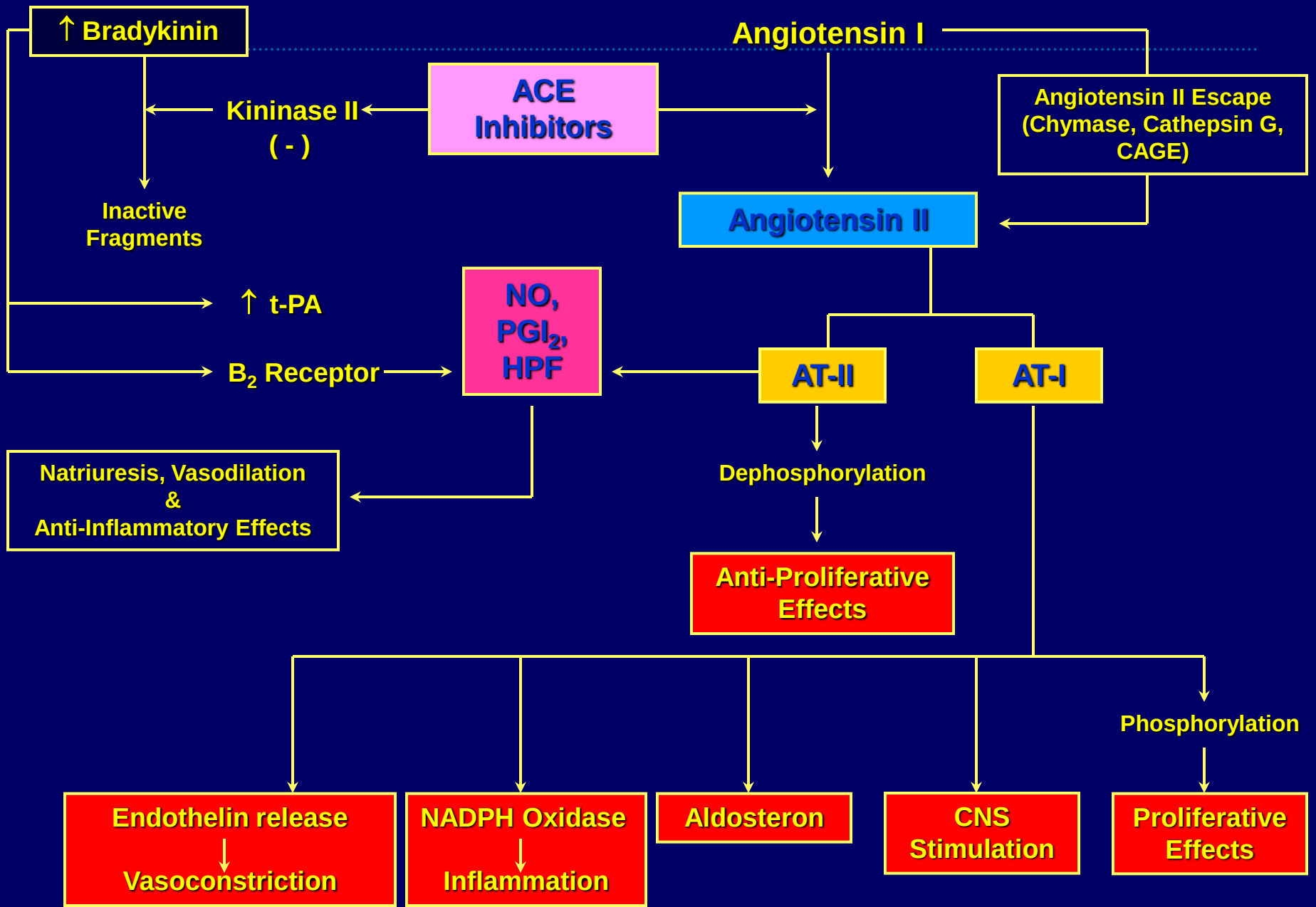
PICO QUESTIONS

- *Is the use of ACEIs/ARBs as compared to other classes better in diabetic hypertensive proteinuric A4 patient?*
- *Is the use of ACEIs/ARBs as compared to other classes better in diabetic kidney disease both type 1 & 2?*
- *Is the use of ACEIs/ARBs as compared to others better in non diabetic non proteinuric hypertensive CKD patient?*
- *Is the use of ACEIs/ARBs as compared to others better in non diabetic proteinuric hypertensive CKD patient?*
- *Is the use of ACEIs/ARBs as compared to other classes better in PKD patient?*

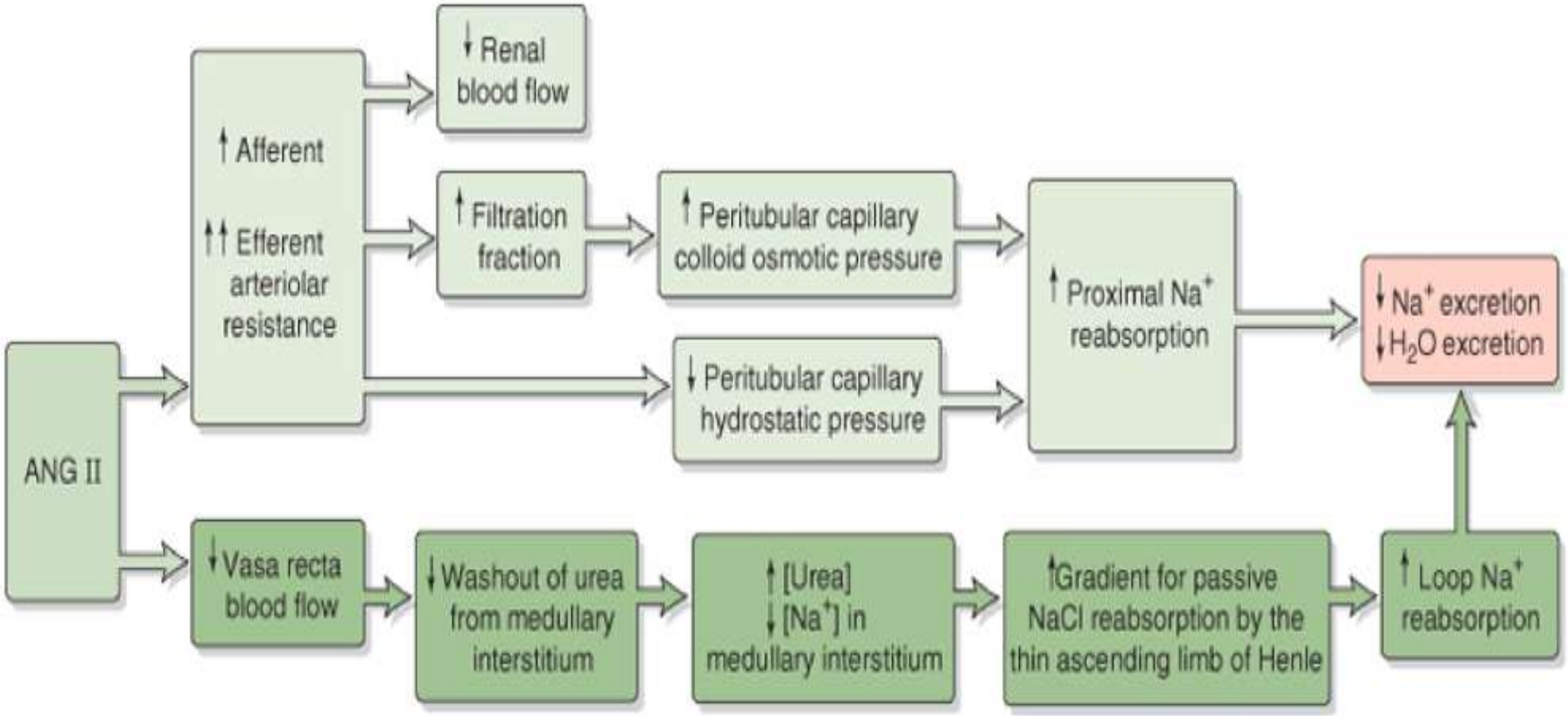
PICO QUESTIONS

- *Is the use of ACEIs/ARBs as compared to other classes better in cardio-renal patient?*
- *Is the use of ACEIs compared to ARBs better in any of the previously mentioned patient subsets?*
- *Is the use of ACEIs & ARBs together as compared to either agents alone better in any of the previously mentioned patient subsets?*
- *Is the use of ACEIs/ARBs as compared to other classes better in hemodfialysis patient?*
- *Is the use of ACEIs/ARBs as compared to other classes better in transplanted patient?*

BIOLOGICAL EFFECTS OF RAAS



ANGII - key regulator of renal equilibrium and renal FEEDBACK loops



JNC-8 Recommendations

	BP thresholds	Goals
✓ *Recommendation* **1** *(Strong recommendation)* **General population ≥60 years**	**SBP ≥150 mm Hg or DBP ≥90 mm Hg**	**SBP <150 mm Hg and DBP <90 mm Hg**
✓ *Recommendation* **2** *(Strong recommendation)* **General population <60 years**	**DBP ≥90 mm Hg**	**DBP <90 mm Hg**
✓ *Recommendation* **3** *(Expert opinion)* **General population <60 years**	**SBP ≥140 mm Hg**	**SBP <140 mm Hg**

JAMA. doi:10.1001/jama.2013.284427. Published online December 18, 2013.

Recommendations

	BP thresholds	Goals
✓ *Recommendation* **4** *(Expert opinion)*		
Population with CKD ≥18 years	**SBP ≥140 mm Hg or DBP ≥90 mm Hg**	**SBP <140 mm Hg and DBP <90 mm Hg**
✓ *Recommendation* **5** *(Expert opinion)*		
Population with diabetes ≥18 years	**SBP ≥140 mm Hg or DBP ≥90 mm Hg**	**SBP <140 mm Hg and DBP <90 mm Hg**
✓ *Recommendation* **6** *(Moderate recommendation)*		
General nonblack population *(with diabetes)*	**Initial treatment**	
	Thiazide-type diuretic, CCB, ACEI, Or ARB.	

JAMA. doi:10.1001/jama.2013.284427. Published online December 18, 2013.

Recommendations

✓ *Recommendation* **7**

(Moderate recommendation)

General *(with diabetes)* black population

Initial treatments

Thiazide-type diuretic, or calcium channel blocker (CCB)

✓ *Recommendation* **8**

(Moderate recommendation)

Population with CKD ≥18 years

Initial or add-on treatments

ACEI, Or ARB

✓ *Recommendation* **9**

(Expert opinion)

Goal BP not reached within a month of treatment

Non control strategies

Increase the dose of the initial drug, or add a second drug *(from the list provided)*

Goal BP not reached with 2 drugs

Add and titrate a third drug *(from the same list)*
Do not use an ACEI and an ARB together in the same patient

JAMA. doi:10.1001/jama.2013.284427. Published online December 18, 2013.

2013 KDIGO: Management of progression and complications of CKD

3.1.5: We suggest that in both diabetic and non-diabetic adults with CKD and with urine albumin excretion of ≥30 mg/24 hours (or equivalent*) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. *(2D)*

3.1.6: We suggest that an ARB or ACE-I be used in diabetic adults with CKD and urine albumin excretion 30-300 mg/24 hours (or equivalent*). *(2D)*

3.1.7: We recommend that an ARB or ACE-I be used in both diabetic and non-diabetic adults with CKD and urine albumin excretion >300 mg/24 hours (or equivalent*). *(1B)*

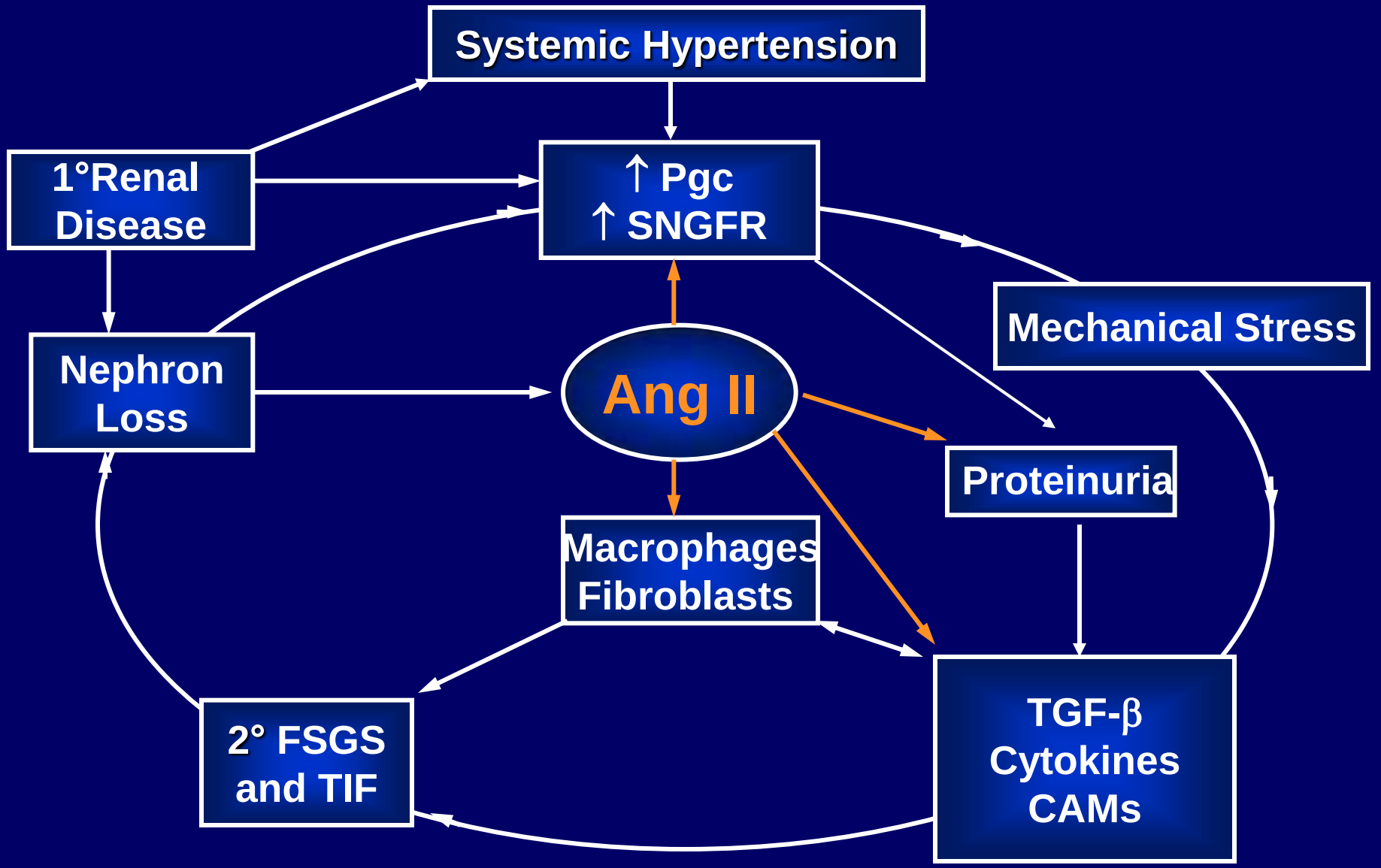
3.1.8: There is insufficient evidence to recommend combining an ACE-I with ARBs to prevent progression of CKD. *(Not Graded)*

KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3:136-150. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf Accessed February 26, 2013

Table 144. Summary of Use of ACE Inhibitors and ARBs in CKD

1.	Indications	• Diabetic kidney disease • Nondiabetic kidney disease with spot urine total protein-to-creatinine ratio >200 mg/g • Consider in kidney transplant recipients with spot urine total protein-to-creatinine ratio >500-1,000 mg/g
2.	Doses Used in Controlled trials (mg/d)	• ACE inhibitors (benazepril 30, captopril 100, lisinopril 20, perindopril 4, ramipril 10, trandolopril 3) • ARBs (candesartan 16, irbesartan 300, losartan 100, valsartan 160)
3.	Side-Effects	• Hypotension, early decrease in GFR, hyperkalemia, cough, angioneurotic edema, rash, contraindicated in 2nd and 3rd trimesters of pregnancy (recommend contraception to women of child-bearing age)
4.	Causes of Early Decrease in GFR	• ECF volume depletion, hypotension, renal artery disease (bilateral or unilateral with a solitary kidney)
5.	Causes of Hyperkalemia	• Increased potassium intake (high potassium foods, supplements, herbal supplements, transfusions, salt substitutes) • Metabolic acidosis • Acute GFR decline • Drugs (beta-blockers, heparin, NSAID, Cox 2 inhibitors, heparin, digoxin overdose, potassium supplements, herbal supplements, potassium-sparing diuretics, cyclosporine, tacrolimus, pentamidine, trimethoprim, lithium. • Laboratory error
6.	Frequency of Monitoring for Side Effects (Blood Pressure, GFR, Serum Potassium)	• If SBP <120 mm Hg, GFR <60 mL/min/1.73 m^2, change in GFR ≥15%, or serum potassium >4.5 mEq/L, – ≤4 weeks after initiation or increase in dose, or – 1-6 months after blood pressure is at goal and dose is stable.
7.	Conditions in which ACE Inhibitors or ARBs Should Not be Used or Used with Caution	• Pregnancy • History of cough, angioedema or other allergic reaction • Bilateral renal artery stenosis • Serum potassium >5.5 mEq/L despite treatment • GFR decline >30% within 4 months without explanation

CKD Progression



Interventions for Slowing CKD Progression

- *Lower BP to <130/80 (JNC-8 <140/90) (RAAS blockers)*
- *Minimise proteinuria (<1g/day) (RAAS blockers)*
- *Moderate dietary protein intake*
- *Weight loss if obese*
- *Smoking cessation*

ANTIHYPERTENSIVE CRITERIA in CKD patients

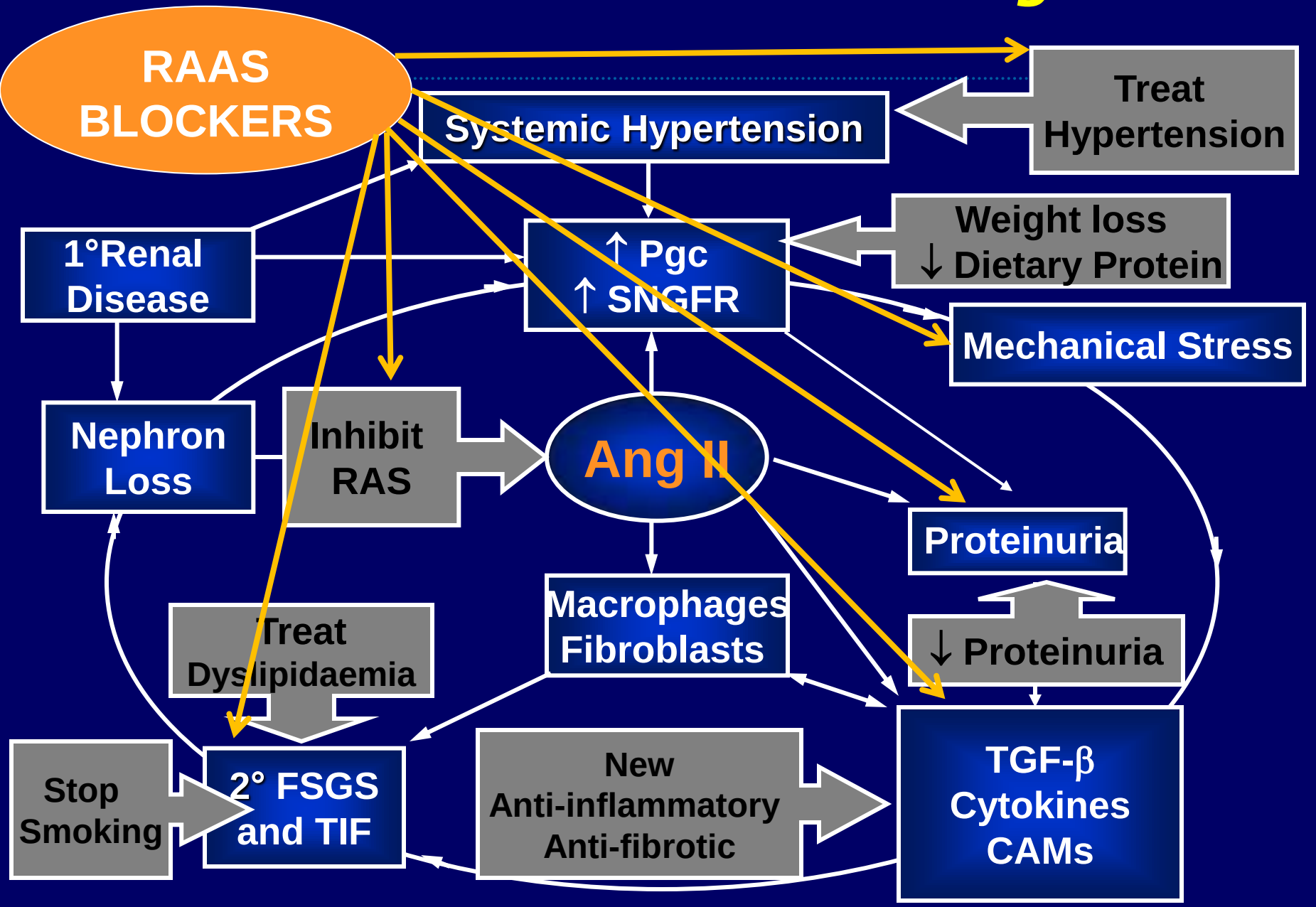
1- Hypertension

2-Proteinuria

3 -Decrease CKD progression

4-Cardiovascular protection

Interventions to Slow CKD Progression



ACEI or ARB in CKD – clinical practice

Creatinine rise

- *Predicts greater renoprotective efficacy*
- *Allow up to 30% ↑ if not progressive*
- *Contraindicated in bilateral RAS*
- *Omit diuretics for 1-2 days*
- *Avoid NSAIDs*
- *Start low dose*
- *Check serum creatinine at 1 week*

Hyperkalaemia

- *Incidence of uncontrolled hyperkalaemia 0-4% in 6 large studies*
- *Dietary advice*
- *Avoid K-sparing diuretics*

Reappraise the Evidence

Paper: *Lancet* 1997; 349; 1857-63.

THE LANCET

Articles

Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy

*The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia)**

cited 902 times!

Summary

Background In diabetic nephropathy, angiotensin-converting-enzyme (ACE) inhibitors have a greater effect than other antihypertensive drugs on proteinuria and the progressive decline in glomerular filtration rate (GFR). Whether this difference applies to progression of non-diabetic proteinuric nephropathies is not clear. The Ramipril Efficacy In Nephropathy study of chronic non-diabetic nephropathies aimed to address whether glomerular protein traffic influences renal-disease progression, and whether an ACE inhibitor was superior to conventional treatment, with the same blood-pressure control, in reducing proteinuria, limiting GFR decline, and preventing endstage renal disease.

Methods In this prospective double-blind trial, 352 patients were classified according to baseline proteinuria (stratum 1: 1–3 g/24 h; stratum 2: ⩾3 g/24 h), and randomly assigned ramipril or placebo plus conventional antihypertensive therapy targeted at achieving diastolic blood pressure under 90 mm Hg. The primary endpoint was the rate of GFR decline. Analysis was by intention to treat.

Background premise (*taken as paradigm*): ACE inhibitors have greater reno-protective effects than other anti-HTN medications in diabetic nephropathy.

Study Question: are ACE inhibitors reno-protective in non-diabetic nephropathy in addition to their anti-HTN effects?

Study Type: prospective double-blinded randomized trial, i.e. *gold standard*, with several hundred participants (*decently powered - random events take on robust Gaussian distributions around 500 events*).

Variable	Ramipril (n=78)	Placebo (n=88)	p*
Mean (SD) age in years	48·9 (13·6)	49·7 (13·6)	0·76
Sex			
Male	66 (85%)	64 (73%)	0·06
Female	12 (15%)	24 (27%)	
Renal disease (number of patients)			
Glomerular	50 (64%)	53 (60%)	0·93
Interstitial, polycystic	4 (5%)	5 (6%)	
Other, unknown	24 (31%)	30 (34%)	
Mean (SD) renal-function indicators			
GFR (mL/min per 1·73 m²)	40·2 (19·0)	37·4 (17·5)	0·35
Creatinine clearance (mL/min per 1·73 m²)	47·3 (21·7)	43·7 (20·4)	0·24
Serum creatinine (μmol/L)†	212 (88)	212 (88)	0·48
Urinary protein excretion (g/24 h)‡	5·6 (2·8)	5·1 (2·0)	0·38
Urinary urea nitrogen excretion (mmol/24 h)§	357 (343)	328 (143)	0·26
Urinary sodium excretion (mmol/24 h)	211·2 (161·2)	198·9 (92·8)	0·65
Mean (SD) arterial blood pressure (mm Hg)			
Systolic	149·8 (17·8)	148·0 (17·3)	0·43
Diastolic	92·4 (11·5)	91·3 (11·1)	0·45
Mean	111·5 (12·2)	110·2 (11·6)	0·41
Number of patients with hypertension			
All with hypertension¶	67 (86%)	77 (88%)	0·80
On hypertensive therapy	58 (74%)	70 (80%)	0·42
Mean (SD) serum biochemistry			
Serum cholesterol (mmol/L)**	6·79 (2·12)	6·63 (1·60)	0·94
Serum tryglycerides (mmol/L)††	2·63 (0·92)	2·35 (1·40)	0·91
Serum potassium (mmol/L)	4·4 (0·6)	4·5 (0·6)	0·28

*p values based on Fisher's exact test for categorical variables and on Wilcoxon test for continuous variables.
†To convert to mg/dL divide by 88·4.
‡Urinary protein excretion is mean of last two measurements before randomisation.
§To convert to g/24 h divide by 35·7.
¶Patients who had sitting systolic or diastolic blood pressure above 140/90 mm Hg or were receiving antihypertensive therapy were regarded as hypertensive.
**To convert to mg/dL divide by 0·02586.
††To convert to mg/dL divide by 0·01129.

Table 1: **Clinical characteristics of stratum 2 study population at time of randomisation***

Exclusion Criteria: insulin dependent DM, coronary artery disease (NSTEMI/STEMI in last 6 months), tx w/ corticosteroids, immunosuppressive drugs, or NSAIDS, uncontrolled blood pressure (diastolic >115 or systolic >220), evidence or suspicion of renovascular disease (~35% of CHF patients have RVD), obstructive uropathy (BPH), cancer, liver disease, chronic cough (asthma, COPD).

VERY BROAD EXCLUSION CRITERIA

Many patients who we might place or think or placing on ACE inhibitors for renal disease as diagnosed by protein urea are patients who have cardiac and pulmonary disease and have a very large probability of using NSAIDS especially aspirin since cardiac patients are placed on aspirin as a prophylactic.

As clinicians we need to keep in mind the often very narrow sample space that studies probe. An excellent study, such as this one, does not mean its conclusions are broadly applicable.

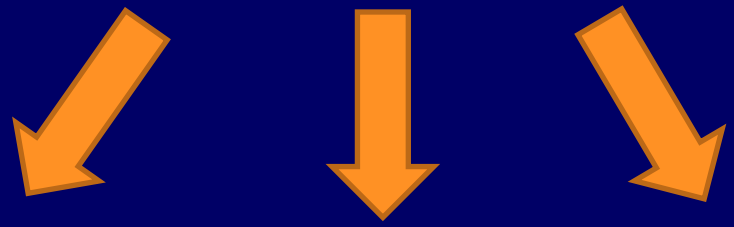
Proteinuria & The renoprotective effect !

- *Proteinuria: A Surrogate Endpoint*

- *Surrogate Endpoint means: a biomarker intended to substitute for a clinical endpoint, biomarkers are often cheaper and easier to measure than 'true' endpoints as morbidity , the need for RRT and mortality … etc.*

- *Can Proteinuria as a surrogate endpoint be used as a replacement for hard endpoints in nephrology clinical research?*

Reduction of proteinuria was associated with:



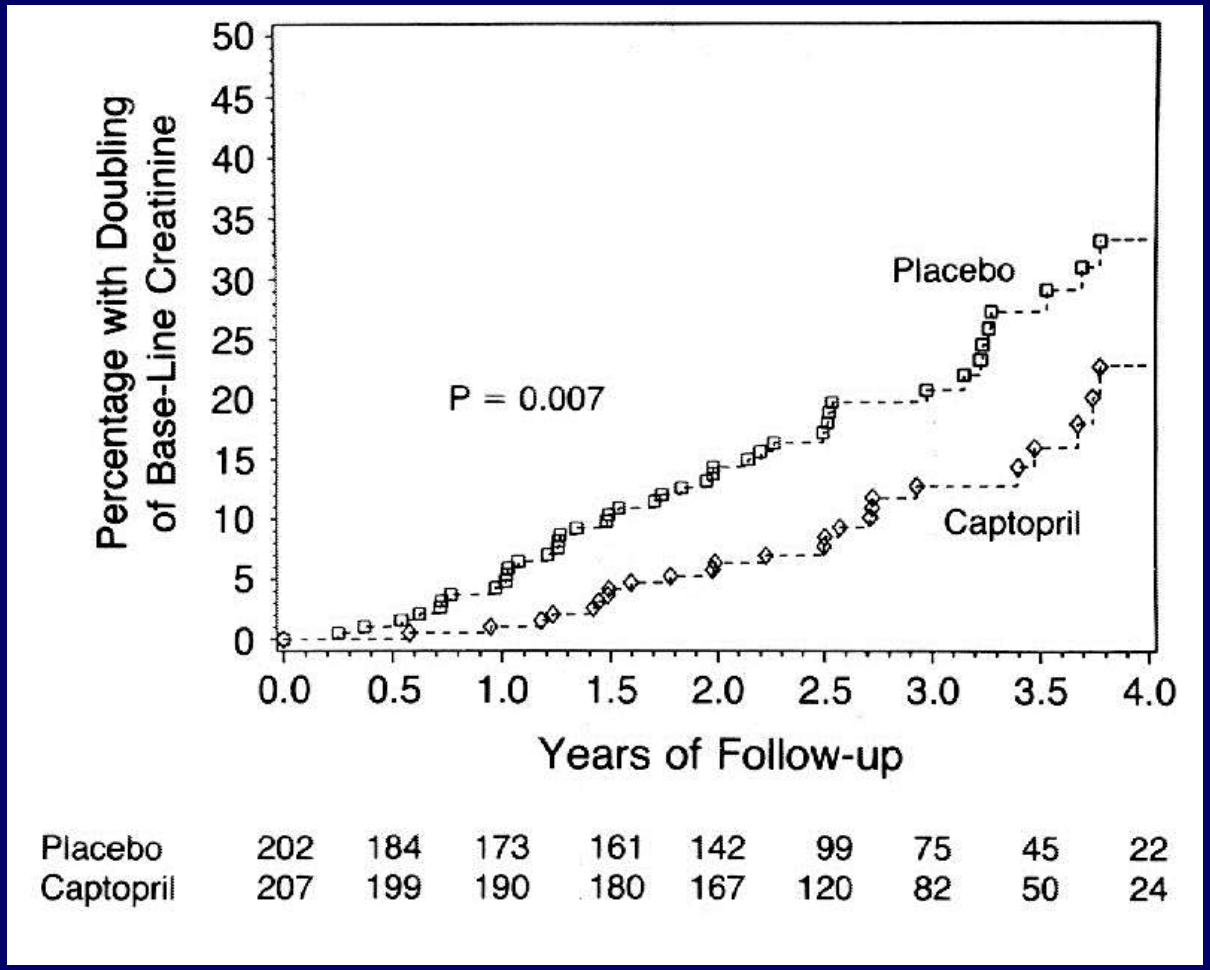
Improved renal function In RENAAL

Unchanged Renal functions In ACCORD BP trial

Worsening of renal Functions in the ONTARGET trial

In fact, RAS inhibitors acquired its renoprotective effect from reducing proteinuria, which is a surrogate marker of renal functions.

ACE-I in type 1 DM.



- RCT
- Lewis et al 1993
- 409 type 1 DM with proteinuria > 500 mg/day.
- Captopril Vs Placebo
- Captopril was proved to protect against deterioration in renal function in insulin-dependent diabetic nephropathy and is significantly more effective than blood pressure control alone.

Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N. Engl. J. Med. 1993;329(20):1456–62.

Characteristic	Captopril (N = 207)	Placebo (N = 202)	P Value†
Age (yr)	35±7	34±8	0.46
Male sex (%)	52	54	0.69
Race (%)			
White	91	87	0.12
Black	5	10	
Duration of diabetes (yr)	22±7	22±7	0.96
Hypertension (%)‡	75	76	0.91
Antihypertensive therapy (%)	60	59	0.84
Systolic blood pressure (mm Hg)§	137±19	140±20	0.21
Diastolic blood pressure (mm Hg)§	85±11	86±12	0.47
Mean arterial pressure (mm Hg)§	102±12	104±13	0.25
Serum creatinine (mg/dl)¶	1.3±0.4	1.3±0.4	0.54
24-Hour urinary protein excretion (mg/day)	2500±2500	3000±2600	0.02
24-Hour urinary urea nitrogen (g/day)‖	11±5	10±5	0.08
24-Hour creatinine clearance (ml/min)	84±46	79±35	0.50
Glycosylated hemoglobin (%)	11.8±2.8	11.6±2.8	0.75

*Plus–minus values are means ±SD.

†For categorical variables the P values were based on Fisher's exact test. The P values for continuous variables were based on the Wilcoxon test.

‡Hypertension was defined as a systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg.

§Blood pressure was measured in seated, resting patients during an office visit.

¶To convert serum creatinine values to micromoles per liter, multiply by 88.4.

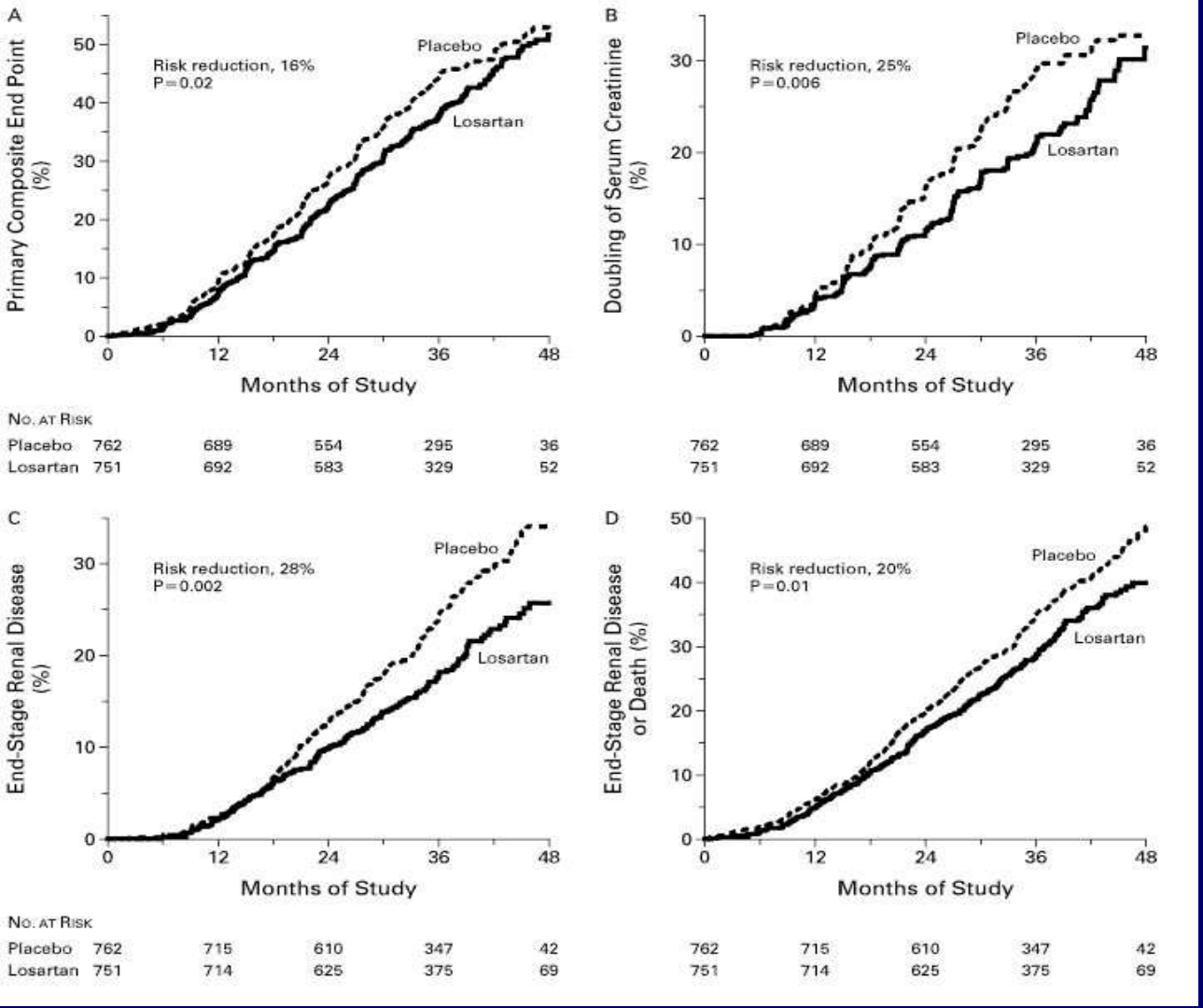
‖To convert urinary urea nitrogen values to millimoles per day, multiply by 35.7.

Randomization Bias

*placebo group had much **worse prognosis** from onset as it had*

- *much more severe albuminuria*
- *a significant difference in BP control systolic and diastolic in those treated by Captopril*
- *Statistics were applied to make the effect independent of blood pressure control.*
- ***Is the renoprotective effect really independent from BP control ?***

ARBs in type 2 DM RENAAL study (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan)



- *RCT*
- *1513 HT type 2 NIDDM.*
- *Losartan Vs Placebo.*
- *Losartan reduced the incidence of doubling of serum creatinine by 25 percent and end-stage renal disease (ESRD) by 28 percent.*

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	LOSARTAN GROUP (N=751)	PLACEBO GROUP (N=762)
Age — yr	60±7	60±7
Sex — no. (%)		
Male	462 (61.5)	494 (64.8)
Female	289 (38.5)	268 (35.2)
Race or ethnic group — no. (%)		
Asian	117 (15.6)	135 (17.7)
Black	125 (16.6)	105 (13.8)
White	358 (47.7)	378 (49.6)
Hispanic	140 (18.6)	136 (17.8)
Other	11 (1.5)	8 (1.0)
Body-mass index†	30±6	29±6
Blood pressure — mm Hg		
Systolic	152±19	153±20
Diastolic	82±10	82±11
Mean arterial‡	105.5±10.9	106.0±11.6
Pulse§	69.4±17.4	70.8±18.1
Medical history — no. (%)		
Use of antihypertensive drugs	693 (92.3)	721 (94.6)
Angina pectoris	65 (8.7)	75 (9.8)
Myocardial infarction	75 (10.0)	94 (12.3)
Coronary revascularization procedure	1 (0.1)	1 (0.1)
Stroke	8	1 (0.1)
Lipid disorder	234 (31.2)	271 (35.6)
Amputation	65 (8.7)	69 (9.1)
Neuropathy	375 (49.9)	379 (49.7)
Retinopathy	494 (65.8)	470 (61.7)
Current smoking	147 (19.6)	130 (17.1)
Laboratory variables		
Median urinary albumin:creatinine ratio	1237	1261
Serum creatinine — mg/dl¶	1.9±0.5	1.9±0.5
Serum cholesterol — mg/dl‖		
Total	227±56	229±55
Low-density lipoprotein	142±47	142±45
High-density lipoprotein	45±16	45±15
Serum triglycerides — mg/dl**	213±180	225±200
Hemoglobin — g/dl††	12.5±1.9	12.5±1.8
Glycosylated hemoglobin — %	8.5±1.7	8.4±1.6

*Plus–minus values are means ±SD. The differences between the treatment groups were not statistically significant.

†Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡The mean arterial pressure was calculated as diastolic arterial pressure + (systolic arterial pressure − diastolic arterial pressure) ÷ 3.

§The pulse pressure was calculated as systolic arterial pressure − diastolic arterial pressure.[11]

¶To convert values to micromoles per liter, multiply by 88.4.

‖To convert values to millimoles per liter, multiply by 0.02586.

**To convert values to millimoles per liter, multiply by 0.01129.

††To convert values to millimoles per liter, multiply by 0.6206.

Again,

Randomization Bias:

- *Placebo group had more patients with angina, myocardial infarctions and lipid disorders.*

TABLE 3. INCIDENCE OF THE PRIMARY COMPOSITE END POINT AND ITS COMPONENTS.*

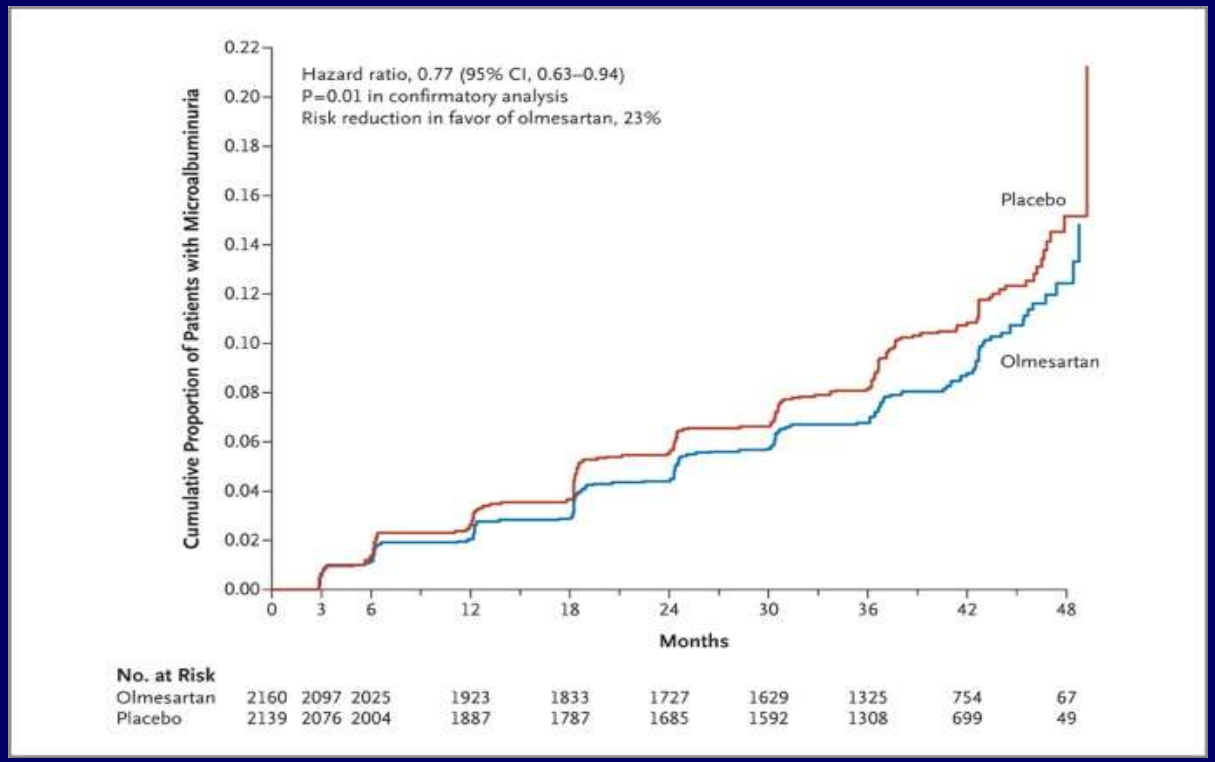
END POINT	LOSARTAN GROUP (N=751)		PLACEBO GROUP (N=762)		P VALUE	RISK REDUCTION
	no. (%)	no./100 patient-yr	no. (%)	no./100 patient-yr		% (95% CI)
Primary composite end point†	327 (43.5)	15.9	359 (47.1)	18.1	0.02	16 (2 to 28)
Doubling of serum creatinine concentration	162 (21.6)	7.9	198 (26.0)	10.0	0.006	25 (8 to 39)
End-stage renal disease	147 (19.6)	6.8	194 (25.5)	9.1	0.002	28 (11 to 42)
Death	158 (21.0)	6.8	155 (20.3)	6.6	0.88	−2 (−27 to 19)
End-stage renal disease or death	255 (34.0)	11.7	300 (39.4)	14.1	0.01	20 (5 to 32)
Doubling of serum creatinine concentration and end-stage renal disease	226 (30.1)	11.0	263 (34.5)	13.2	0.01	21 (5 to 34)

*In end-point trials, there is often a difference between the risk reduction as determined on the basis of the Cox regression model and the risk reduction as determined on the basis of the crude rates of events. The difference results in part from the fact that the Cox regression model accounts for the time at risk — i.e., the longer average follow-up in the losartan group than in the placebo group. To address this aspect of the difference, we present the numbers of events per 100 patient-years of follow-up. In addition, the Cox model accounts for the base-line level of proteinuria (which was a stratification factor) and the geographic region, as prespecified in the data analysis plan. CI denotes confidence interval.

†The primary end point was a composite of a doubling of the serum creatinine concentration, end-stage renal disease, or death.

- *Mortality didn't differ between the two groups !!!*

ROADMAP Study



- *RCT double blinded.*
- *4447 patients with type 2 DM.*
- *Olmesartan Vs Placebo.*
- *primary outcome was the time to the first onset of MA.*
- *olmesartan was associated with a delayed onset of MA, even though blood-pressure control in both groups was excellent according to current standards.*

Haller H, Ito S, Izzo JL, Januszewicz A, Katayama S, Menne J, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N. Engl. J. Med. 2011;364(10):907–17.

Table 2. Secondary Efficacy End Points during the Double-Blind Treatment Period.*

End Point	Olmesartan (N=2232)	Placebo (N=2215)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Composite of cardiovascular complications or death from cardiovascular causes	96 (4.3)	94 (4.2)	1.00 (0.75–1.33)	0.99
Composite of death from any cause	26 (1.2)	15 (0.7)	1.70 (0.90–3.22)	0.10
Death from cardiovascular causes	15 (0.7)	3 (0.1)		
Death not related to cardiovascular causes	8 (0.4)	10 (0.5)		
Death from unknown cause	3 (0.1)	2 (0.1)		
Composite of death from cardiovascular causes	15 (0.7)	3 (0.1)	4.94 (1.43–17.06)	0.01
Sudden cardiac death	7 (0.3)	1 (<0.1)		
Death due to fatal myocardial infarction	5 (0.2)	0		
Evidence of recent myocardial infarction on autopsy	0	0		
Death due to congestive heart failure	0	0		
Death during or after percutaneous transluminal coronary angioplasty or CABG	1 (<0.1)	0		
Death due to fatal stroke	2 (0.1)	2 (0.1)		
Composite of cardiovascular complications, excluding new-onset atrial fibrillation and transient ischemic attack	63 (2.8)	71 (3.2)	0.87 (0.62–1.22)	0.42
Composite of new-onset atrial fibrillation or transient ischemic attack	19 (0.9)	28 (1.3)	0.67 (0.37–1.19)	0.17
Composite of all cardiovascular complications	81 (3.6)	91 (4.1)	0.87 (0.65–1.18)	0.37

* All results were based on adjudicated end points. The composite secondary efficacy end points were analyzed with the use of a Cox proportional-hazards regression model with study treatment as the fixed effect. For composite end points, the time to the onset of an event was defined as the time from randomization (date of visit 1) to the first occurrence of any component of the composite end point. CABG denotes coronary-artery bypass grafting.

However,

despite reducing MA, Olmesartan had no effect on cardiovascular morbidity, kidney function and there were significantly ***more deaths*** *in the treatment group!!!*

Combination therapy in type 2 DM ONTARGET STUDY

The combination therapy of ramipril plus telmisartan was compared to monotherapy in diabetic patients, there was no difference in the composite primary outcome, but it was associated with worse renal outcome than monotherapy.

Table 4. Secondary and Other Outcomes.

Outcome	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)	Telmisartan vs. Ramipril	Combination Therapy vs. Ramipril
	number (percent)			*relative risk (95% CI)*	
Revascularization	1269 (14.8)	1290 (15.1)	1303 (15.3)	1.03 (0.95–1.11)	1.04 (0.97–1.13)
Hospitalization for angina	925 (10.8)	954 (11.2)	952 (11.2)	1.04 (0.95–1.14)	1.04 (0.95–1.14)
Worsening or new angina	567 (6.6)	536 (6.3)	538 (6.3)	0.95 (0.84–1.07)	0.96 (0.85–1.08)
New diagnosis of diabetes*	366 (6.7)	399 (7.5)	323 (6.1)	1.12 (0.97–1.29)	0.91 (0.78–1.06)
Any heart failure	514 (6.0)	537 (6.3)	478 (5.6)	1.05 (0.93–1.19)	0.94 (0.83–1.07)
New atrial fibrillation†	570 (6.9)	550 (6.7)	537 (6.5)	0.97 (0.86–1.09)	0.96 (0.85–1.07)
Renal impairment‡	871 (10.2)	906 (10.6)	1148 (13.5)	1.04 (0.96–1.14)	1.33 (1.22–1.44)§
Renal failure requiring dialysis	48 (0.6)	52 (0.6)	65 (0.8)	1.09 (0.74–1.61)	1.37 (0.94–1.98)

Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N. Engl. J. Med. 2008;358(15):1547–59.

ALTITUDE Trial (Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes)

Table 3. Most Commonly Reported Adverse Events and Study-Drug Discontinuation.*

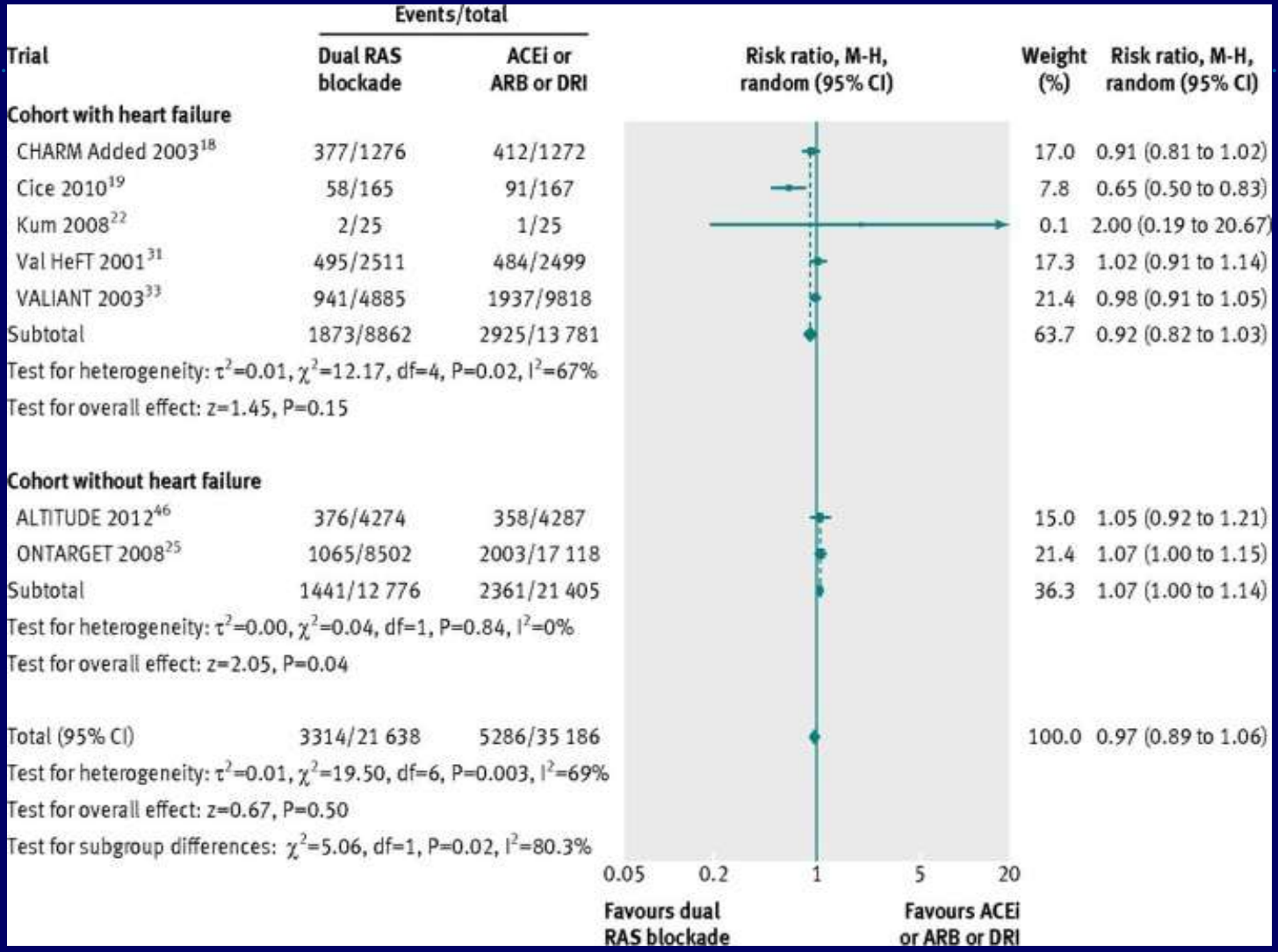
Event	Any Event Reported		P Value	Event Leading to Permanent Study-Drug Discontinuation		P Value
	Aliskiren (N=4272)	Placebo (N=4285)		Aliskiren (N=4272)	Placebo (N=4285)	
	no. of patients (%)			*no. of patients (%)*		
Hyperkalemia	1670 (39.1)	1244 (29.0)	<0.001	205 (4.8)	111 (2.6)	<0.001
Peripheral edema	686 (16.1)	706 (16.5)	0.60	11 (0.3)	7 (0.2)	0.34
Hypotension	519 (12.1)	357 (8.3)	<0.001	28 (0.7)	13 (0.3)	0.02
Diarrhea	417 (9.8)	312 (7.3)	<0.001	11 (0.3)	7 (0.2)	0.34
Hypertension	429 (10.0)	469 (10.9)	0.17	3 (0.1)	9 (0.2)	0.15
Renal impairment	418 (9.8)	371 (8.7)	0.07	65 (1.5)	54 (1.3)	0.30
Nasopharyngitis	405 (9.5)	383 (8.9)	0.39	1 (<0.1)	0	NA
Hypoglycemia	393 (9.2)	341 (8.0)	0.04	1 (<0.1)	3 (0.1)	NA
Back pain	363 (8.5)	353 (8.2)	0.67	1 (<0.1)	2 (<0.1)	NA
Dizziness	327 (7.7)	314 (7.3)	0.57	4 (0.1)	4 (0.1)	NA
Urinary tract infection	326 (7.6)	288 (6.7)	0.10	4 (0.1)	2 (<0.1)	NA
Anemia	316 (7.4)	307 (7.2)	0.68	0	0	—
Pain in extremity	302 (7.1)	317 (7.4)	0.56	1 (<0.1)	2 (<0.1)	NA
Arthralgia	302 (7.1)	313 (7.3)	0.67	0	1 (<0.1)	NA
Cough	265 (6.2)	283 (6.6)	0.45	1 (<0.1)	1 (<0.1)	NA
Bronchitis	242 (5.7)	239 (5.6)	0.86	0	0	—
Dyspnea	223 (5.2)	213 (5.0)	0.60	6 (0.1)	5 (0.1)	0.76
Upper respiratory tract infection	223 (5.2)	229 (5.3)	0.80	1 (<0.1)	0	NA
Cataract	229 (5.4)	223 (5.2)	0.75	0	0	—
Constipation	203 (4.8)	241 (5.6)	0.07	0	1 (<0.1)	NA
Headache	200 (4.7)	220 (5.1)	0.33	2 (<0.1)	4 (0.1)	NA

The trial was stopped prematurely after the second interim efficacy analysis due to higher reported cases of hyperkalemia and hypotension.

Despite a significant reduction in proteinuria and blood pressure, Aliskiren combined with ACE/ARB had no positive effect on any cardio-renal endpoint

Parving H-H, Brenner BM, McMurray JJ V, de Zeeuw D, Haffner SM, Solomon SD, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N. Engl. J. Med. 2012;367(23):2204–13.

A recent meta-analysis (BMJ 2013)s

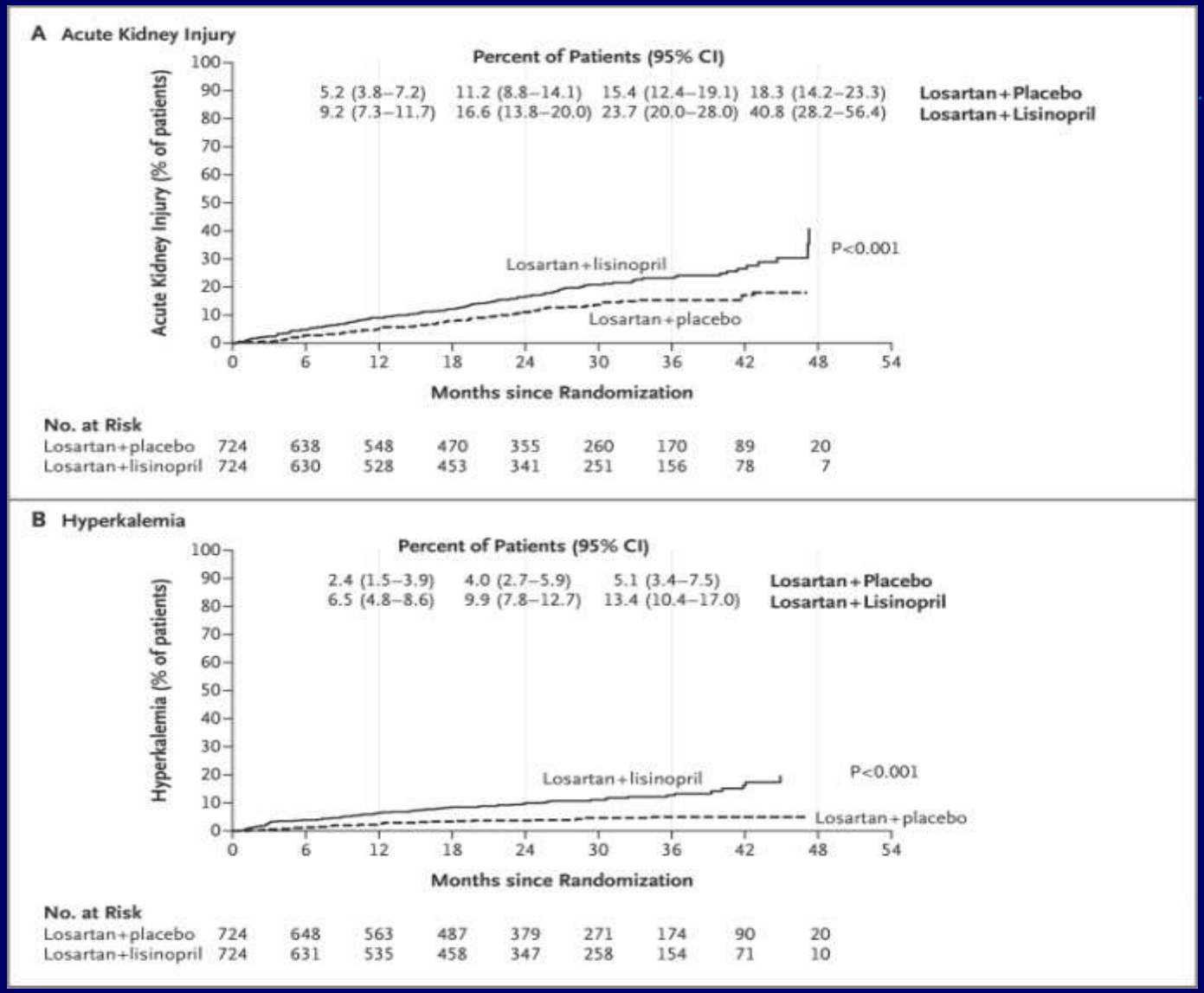


Trial	Events/total: Dual RAS blockade	Events/total: ACEi or ARB or DRI	Weight (%)	Risk ratio, M-H, random (95% CI)
Cohort with heart failure				
CHARM Added 2003[18]	377/1276	412/1272	17.0	0.91 (0.81 to 1.02)
Cice 2010[19]	58/165	91/167	7.8	0.65 (0.50 to 0.83)
Kum 2008[22]	2/25	1/25	0.1	2.00 (0.19 to 20.67)
Val HeFT 2001[31]	495/2511	484/2499	17.3	1.02 (0.91 to 1.14)
VALIANT 2003[33]	941/4885	1937/9818	21.4	0.98 (0.91 to 1.05)
Subtotal	1873/8862	2925/13 781	63.7	0.92 (0.82 to 1.03)
Test for heterogeneity: τ^2=0.01, χ^2=12.17, df=4, P=0.02, I^2=67%				
Test for overall effect: z=1.45, P=0.15				
Cohort without heart failure				
ALTITUDE 2012[46]	376/4274	358/4287	15.0	1.05 (0.92 to 1.21)
ONTARGET 2008[25]	1065/8502	2003/17 118	21.4	1.07 (1.00 to 1.15)
Subtotal	1441/12 776	2361/21 405	36.3	1.07 (1.00 to 1.14)
Test for heterogeneity: τ^2=0.00, χ^2=0.04, df=1, P=0.84, I^2=0%				
Test for overall effect: z=2.05, P=0.04				
Total (95% CI)	3314/21 638	5286/35 186	100.0	0.97 (0.89 to 1.06)
Test for heterogeneity: τ^2=0.01, χ^2=19.50, df=6, P=0.003, I^2=69%				
Test for overall effect: z=0.67, P=0.50				
Test for subgroup differences: χ^2=5.06, df=1, P=0.02, I^2=80.3%				

Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. BMJ. 2013;346:f360.

Dual blockade of the renin-angiotensin failed to reduce mortality and was associated with an excessive risk of adverse events such as hyperkalemia, hypotension, and renal failure when compared with monotherapy. The overall risk to benefit ratio argues against the use of dual therapy.

VA NEPHRON D TRIAL



Combination therapy with an ACE inhibitor and an ARB was associated with an **increased risk of adverse events** among patients with diabetic nephropathy. **AKI and hyperkalemia** were also more in the combination group.

Of remark: this study included 100 % patients with UACR >300 mg/g

Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N. Engl. J. Med. 2013;369(20):1892–903.

So, as you can see from these trials, The use of surrogate markers (as Proteinuria) can be misleading or even damaging

- *Despite reducing proteinuria:*
  1. *In RENAAL : No difference in Mortality.*
  2. *In ROADMAP : More cardiovascular Mortality.*
  3. *In ONTARGET : Faster decline in GFR.*
  4. *In ALTITUDE : More Hyperkalemia and Hypotension.*
  5. *In VA NEPHRON D: More AKI and Hyperkalemia.*

The new england journal of medicine
December 11, 2014 vol. 371 no. 24

Blood Pressure in Early Autosomal Dominant Polycystic Kidney Disease

HALT-PKD Trial Investigators

CONCLUSIONS

- *In early ADPKD, the combination of lisinopril and telmisartan did not significantly alter the rate of increase in total kidney volume. As compared with standard boodpressure control, rigorous blood-pressure control was associated with a slower increase in total kidney volume, no overall change in the estimated GFR, a greater decline in the left-ventricular-mass index, and greater reduction in urinary albumin excretion.*

The new england journal of medicine
December 11, 2014 vol. 371 no. 24

Angiotensin Blockade in Late Autosomal Dominant Polycystic Kidney Disease

HALT-PKD Trial Investigators

CONCLUSIONS

- *Monotherapy with an ACE inhibitor was associated with blood-pressure control in most patients with ADPKD and stage 3 chronic kidney disease. The addition of an ARB did not alter the decline in the estimated GFR.*

FROM PROFESSOR GLASSOCK AT ASN 2014:

- *HALT-PKD- study a showed the a lower BP goal slows rate of increase of total kidney volume (TKV), reduces LVH, reduces albuminuria but has no effect on decline in eGFR (no mGFR reported. Dual ACEi + ARB neither beneficial or harmful. High uncertainty whether the short-term benefits on TKV change and LVH will have a benefit on Survival or ESRD.*

Comments:

- *Disconnect between BP lower targets and reduction in LVH/albuminuria AND PKD progression in terms of decline of eGFR. this raises questions regarding the assumption (made for instance in mTOR inhibitors in ADPKD) that a reduction in TKV (Total Kidney Volume) would translate into slowewr ADPKD progression.*

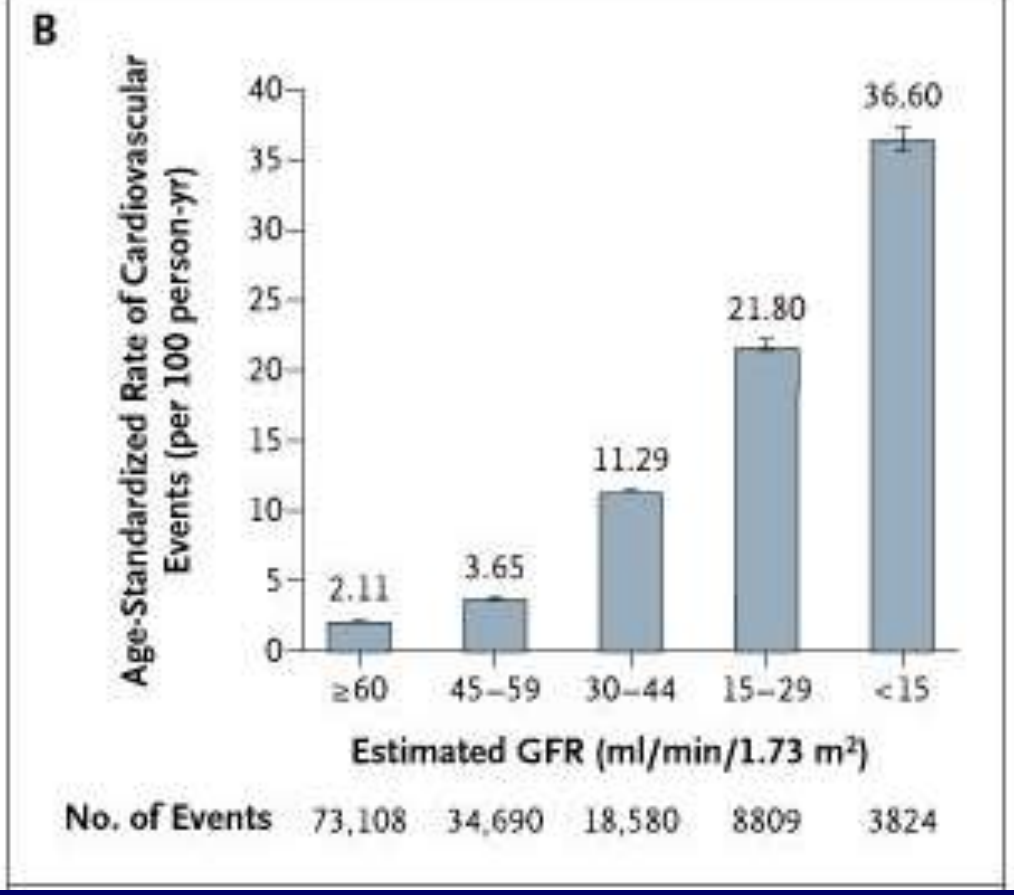
- *Also raises questions regarding the assumption that a reduction in LVH would imrpove CKD survival (by analogy here...a higher hematocrit improves LVH but doesnt survival...).*

- ***Clinical trials in Nephrology are a huge challenge:***

- *1. Surrogate markers are unpredictable at best in terms of outcomes.*
- *2. Hard endpoints would take 5-10 years to reach.*

- *UNLESS, BETTER RISK STRATIFICATION OF THOSE INCLUDED IN RCTs. CHOOSING ESTABLISHED AND PREDICTABLE PROGRESSORS (if possible) WHERE A RESPONSE TO AN INTERVENTION WOULD BE MORE LIKELY.*

CV Risk in CKD



Age-Standardized Rates of Cardiovascular Events According to the Estimated GFR among 1,120,295 Ambulatory Adults

The NEW ENGLAND JOURNAL of MEDICINE

Go, A. S. et al.
NEJM 2004;351:1296-1305

•The commencement of renal impairment in HF patients usually warrant unjustified reduction or holding of the mainstay for therapy of cardiac failure; diuretics and RAAS blockade, under the notion of preventing further deterioration in renal function.

Recognition that elevated serum creatinine portends worse outcomes in HF prompts physicians to be concerned about the renal effects of these agents. However, mean serum creatinine increased even though outcomes were better in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS).

With diuresis, serum creatinine is more likely to increase in patients receiving ACE inhibition and in those with the lowest blood pressures. These data suggest that some increase in creatinine should be tolerated with the use of ACE inhibition, and other interventions (such as decreased diuresis) might be needed to accomplish this.

The advantage of ACE inhibitors in delaying progression and death in HF is undeniable, and their use should be encouraged unless detrimental effects are clearly proven

A proven cardiovascular protective effects ?

- *Ramipril significantly reduces the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure in the HOPE.*

- *And among patients with stable coronary heart disease without apparent heart failure, perindopril can significantly improve outcome in the EUROPA.*

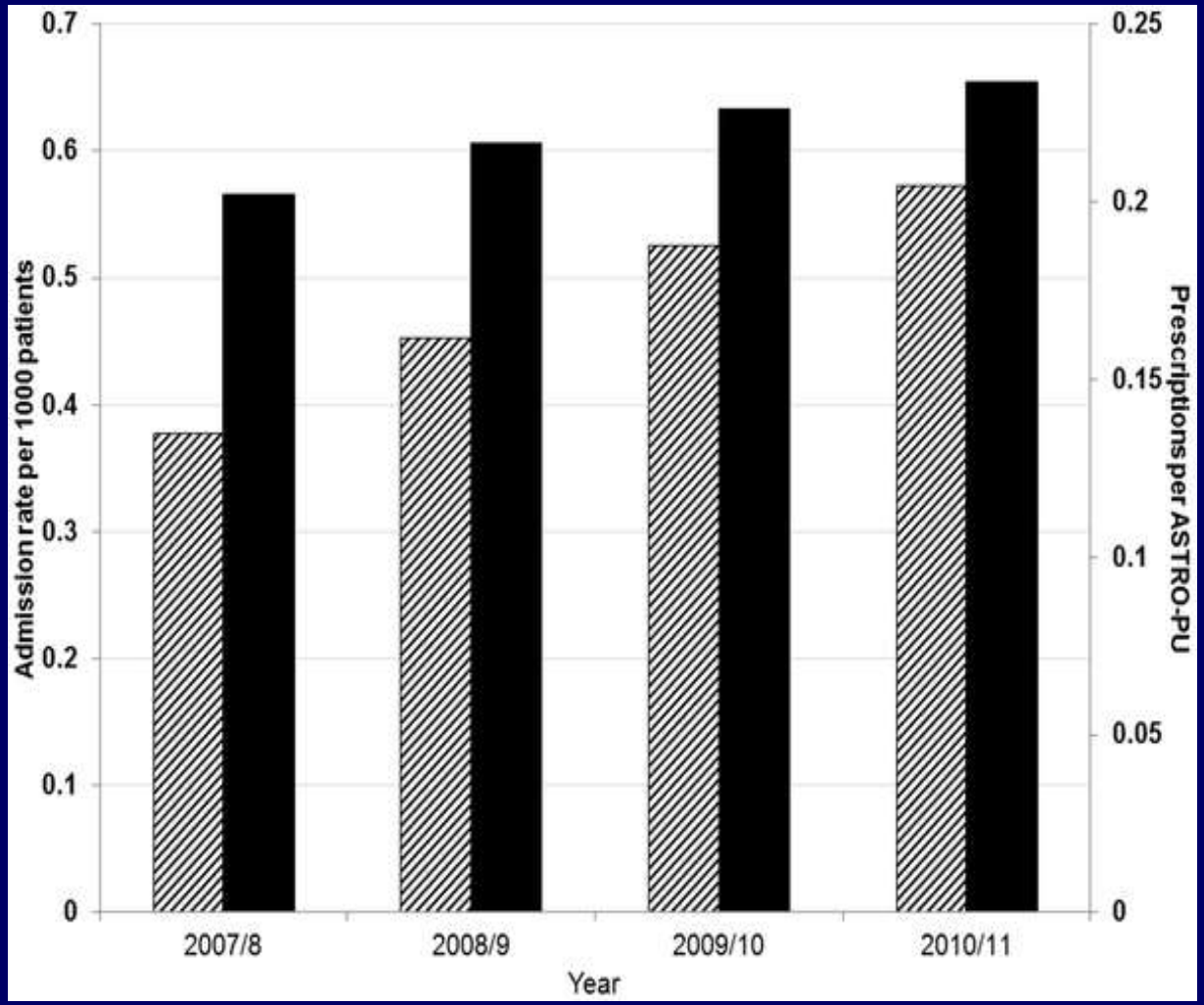
However,

*The extent of cardiac benefits can't be determined whether it is due to ACE inhibitors or to the lower blood pressure, and this was clearly expressed in the **BP LTTC** meta-analysis (Blood Pressure Lowering Treatment Trialists' Collaboration) that shows no cardiovascular protection advantages of RAAS inhibition, but it's rather the blood pressure lowering effect using any commonly-used regimen that reduces the risk of total major cardiovascular events.*

LANCET 2003

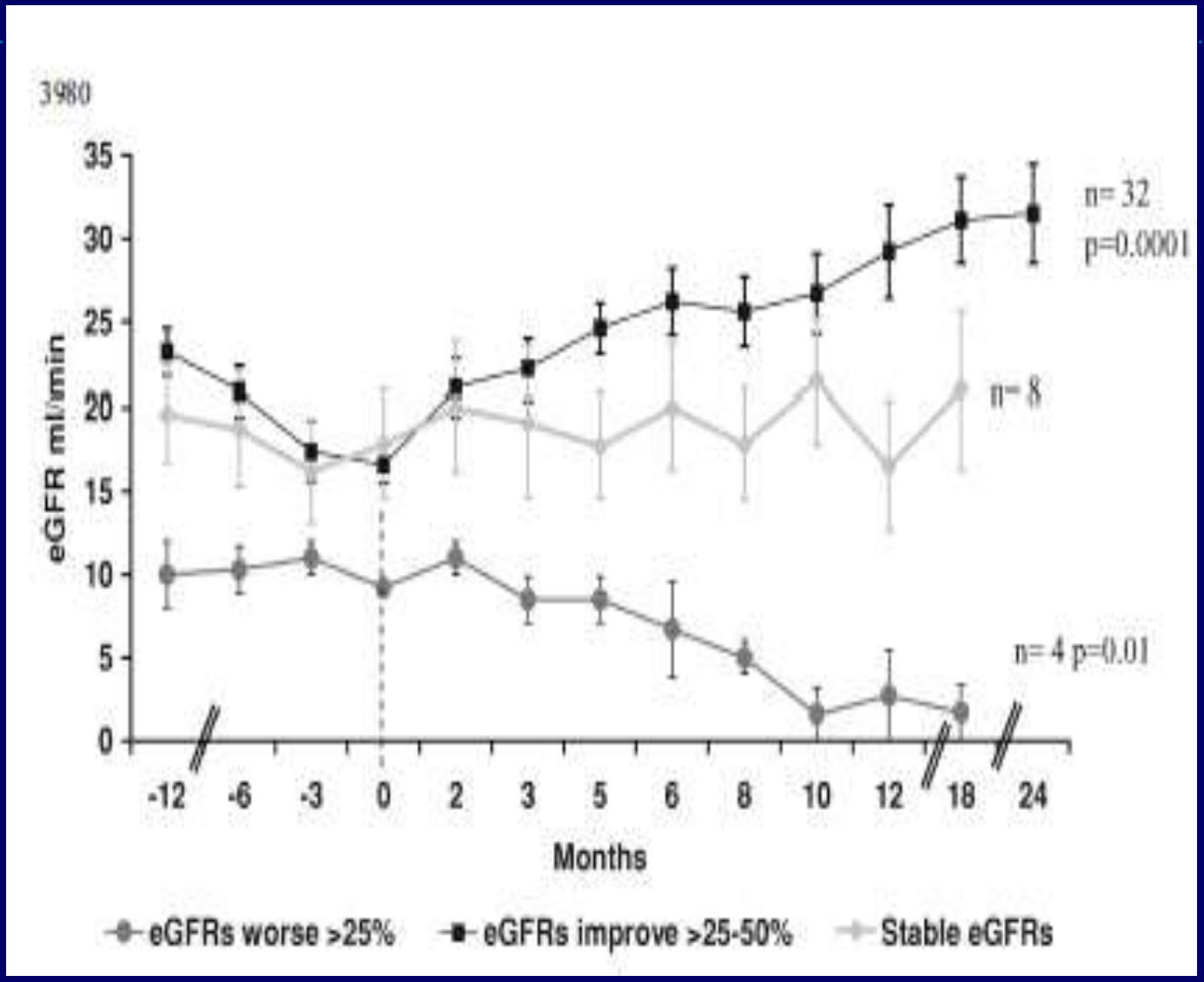
More Side Effects also ???

Increase incidence of AKI was attributed in the UK to increase in the use of ACE inhibitors and ARBs in a recently published UK report.



Tomlinson LA, Abel GA, Chaudhry AN, Tomson CR, Wilkinson IB, Roland MO, et al. ACE inhibitor and angiotensin receptor-II antagonist prescribing and hospital admissions with acute kidney injury: a longitudinal ecological study. PLoS One. 2013;8(11):e78465.

Stop it and your GFR will increase !



Ahmed AK, Kamath NS, El Kossi M, El Nahas AM. The impact of stopping inhibitors of the renin-angiotensin system in patients with advanced chronic kidney disease. Nephrol. Dial. Transplant. 2010;25(12):3977–82.5

So, Is there any beneficial effects of RAAS blockade rather than reduction of blood pressure ?

The benefits of ACE inhibitors or ARBs on renal outcomes in placebo-controlled trials probably ***result only from a blood-pressure-lowering effect****. In patients with diabetes, additional renoprotective actions of these substances beyond lowering blood pressure remain* ***unproven****, and there is uncertainty about the greater renoprotection seen in non-diabetic renal disease.*

Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. ***Lancet.2005****;366(9502):2026–33.*

Small Clinical Advise.

- ***Therefore**, a small advice can guide your way in clinical practice, which is:*
- *Use RAS inhibiting agents in **young** diabetics with microvascular complications, tailor your regimen, or even combine ACEI and ARBs (for experts) in heavy proteinuric patients with careful monitoring.*

- *But, avoid them completely in **older** diabetics with macrovascular complications, atherosclerotic renal artery and ischemic nephropathy. Angiotensin in these people (Type 2 DM) is responsible for maintaining glomerular filtration by inducing some efferent arteriolar vasoconstriction that increase intraglomerular capillary pressure allowing for filtration to be maintained and compensating for decrease in renal perfusion from the atherosclerotic renal arteries.*

- *Also, Avoid using RAAS Blockers in advanced CKD or even stop it !*

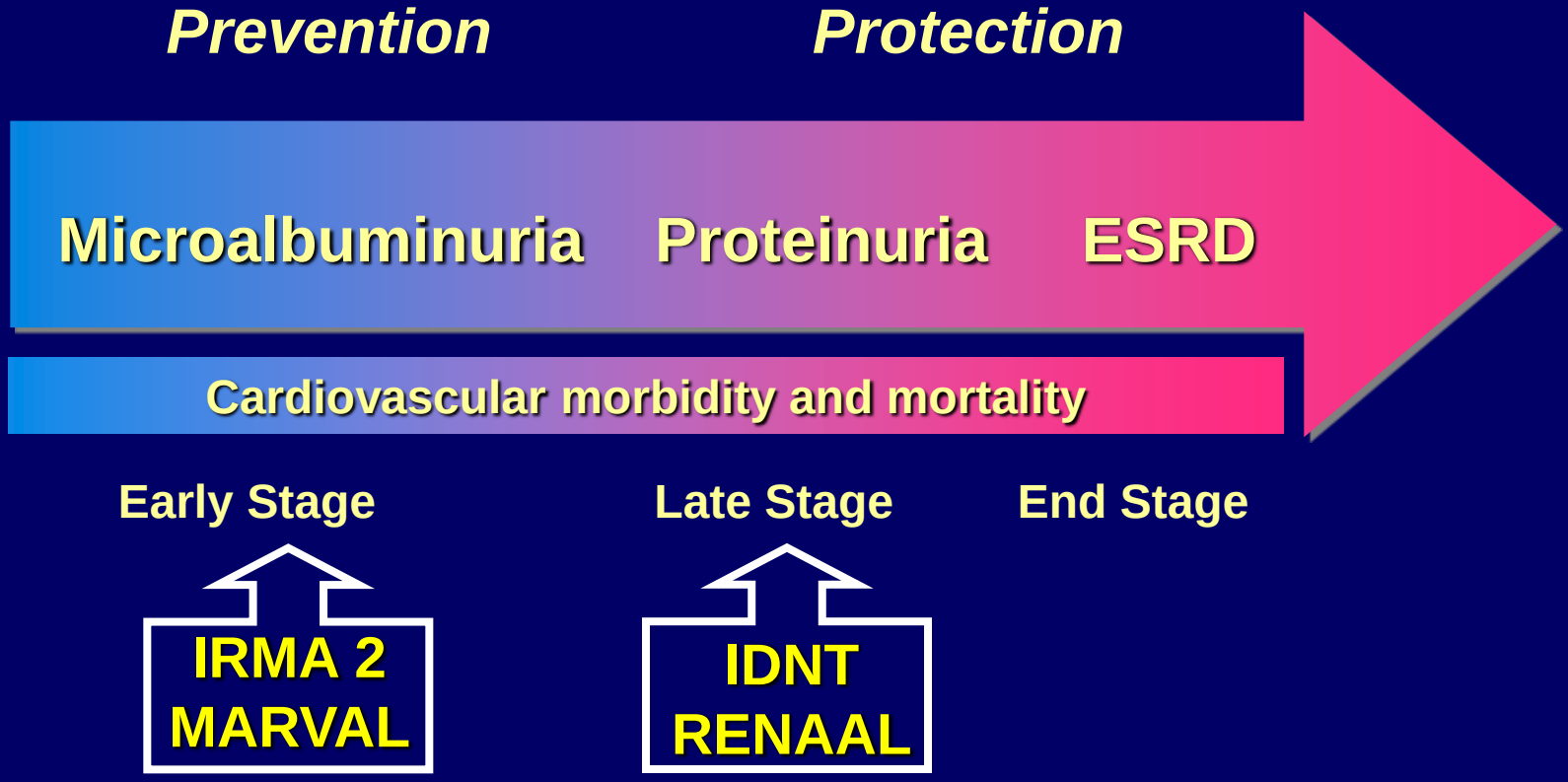
- *Also, Don't be obsessed with reduction of microalbuminuria and proteinuria in CKD (Surrogate marker) and focus of the true hard endpoints of death and ESRD.*


THANK YOU

Reducing CV Risk in CKD

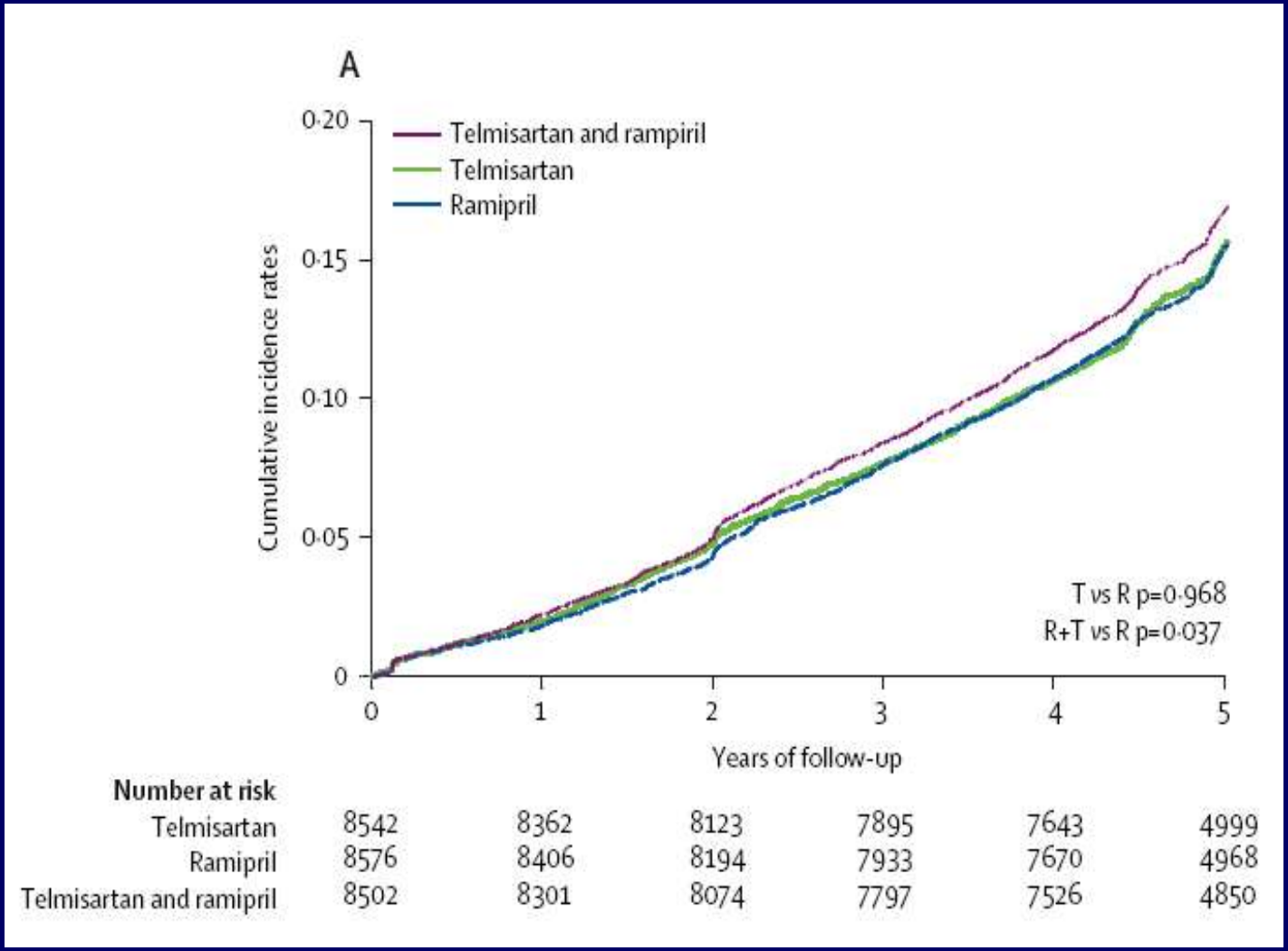
- *Control hypertension (<130/80mmHg)*
- *ACEI or ARB as first choice*
- *Treat dyslipidemia as for "high risk"*
- *Smoking cessation*
- *Aspirin for diabetics and ?others*
- *Ca and phosphate control*

Angiotensin Receptor Antagonists Trials Across The Whole Spectrum Of Type 2 Diabetic Renal Disease Progression



IRMA 2: Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria
MARVAL: Microalbuminuria Reduction with Valsartan
IDNT: Irbesartan Diabetic Nephropathy Trial
RENAAL: Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan
ESRD: End-stage renal disease

Effects of ramipril, telmisartan or both on renal outcomes (dialysis, doubling of serum creatinine, and death) in the ONTARGET trial



Mann et al. The Lancet 2008; 372: 547-553

CONCLUSIONS

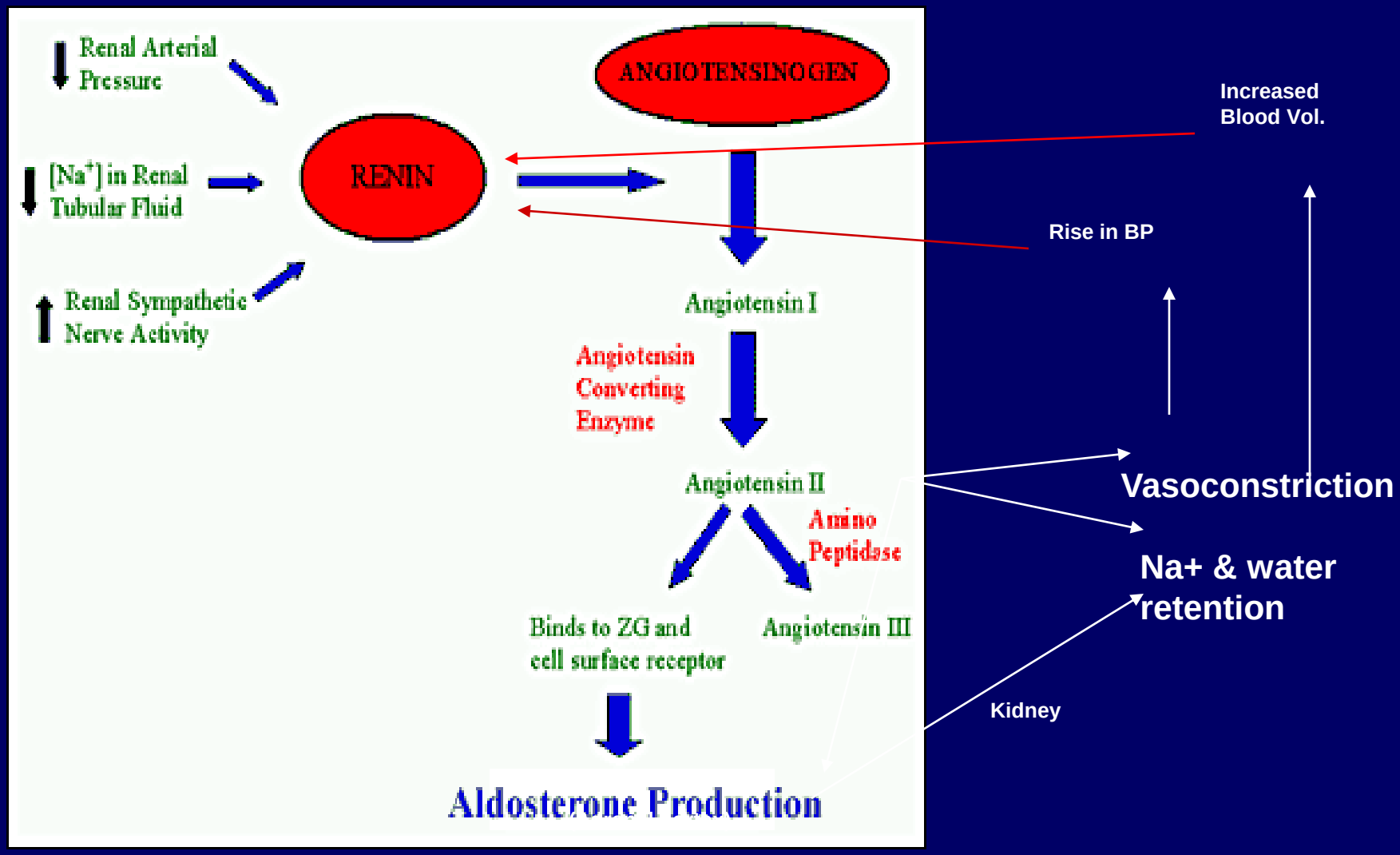
- ARBs (telmisartan) have demonstrated to be as efficacious as ACE-Is in patients at high cardiovascular risk without LV dysfunction, and in patients with post-ischemic (valsartan) and chronic LV systolic dysfunction (valsartan, candesartan)
- ARBs (candesartan, irbesartan) have not demonstrated to be efficacious in patients with LV diastolic dysfunction, similarly to ACE-Is
- ARBs (losartan, valsartan, irbesartan) have demonstrated to provide renal protection in patients with pre-clinical and clinical diabetic nephropathy
- ARBs (candesartan) have demonstrated to induce retinopathy regression in type II diabetics (but needs confirmation)
- Dual RAS blockade was ineffective and potentially harmful in patients without LV dysfunction and this association should be used with caution and strict surveillance of renal function
- Dual RAS blockade (valsartan, candesartan) reduces mortality/morbidity in patients with chronic LV systolic dysfunction

RAAS

- *Renin is a proteolytic enzyme and also called angiotensinogenase*
- *It is produced by juxtaglomerular cells of kidney*
- *It is secreted in response to:*
  - *Decrease in arterial blood pressure*
  - *Decrease Na+ in macula densa*
  - *Increased sympathetic nervous activity*
- *Renin acts on a plasma protein – Angiotensinogen (a glycoprotein synthesized and secreted into the bloodstream by the liver) and cleaves to produce a decapeptide Angiotensin-I*

- *Angiotensin-I is rapidly converted to Angiotensin-II (octapeptide) by ACE (present in luminal surface of vascular endothelium)*
- *Furthermore degradation of Angiotensin-II by peptidases produce Angiotensin-III*
- *Both Angiotensin-II and Angiotensin-III stimulates Aldosterone secretion from Adrenal Cortex (equipotent)*
- *AT-II has very short half life – 1 min*

RAAS - Physiology



RAAS – actions of Angiotensin-II.

1. *Powerful vasoconstrictor particularly arteriolar – direct action and release of Adr/NA release*
   - *Promotes movement of fluid from vascular to extravascular*
   - *More potent vasopressor agent than NA – promotes Na+ and water reabsorption*
   - *It increases myocardial force of contraction (CA++ influx promotion) and increases heart rate by sympathetic activity, but reflex bradycardia occurs*
   - *Cardiac output is reduced and cardiac work increases*
2. *Aldosterone secretion stimulation – retention of Na++ in body*
3. *Vasoconstriction of renal arterioles – rise in IGP – glomerular damage*
4. *Decreases NO release*
5. *Decreases Fibrinolysis in blood*
6. *Induces drinking behaviour and ADH release by acting in CNS – increase thirst*
7. *Mitogenic effect – cell proliferation*

RAAS Inhibitors

1-Angiotensin-Converting Enzyme Inhibitors,

2-Angiotensin Receptor Blockers

3- Direct Renin Inhibitors

RAAS inhibitors are among the best tolerated antihypertensive drugs.

The direct ***renin inhibitor (DRI) aliskiren*** *is one of the newest BP drugs, but there are no completed or ongoing RCTs of aliskiren monotherapy.*

Dual RAS blockade" either with an ACEI plus an ARB or with aliskiren plus an ACEI or ARB—is now contraindicated.

1-More hypotension,

2-Accelerate the decline in renal function,

3-Cause more hyperkalemia .

High levels of circulating prorenin may stimulate A I *receptor–independent signaling pathways, which are both potentially beneficial and potentially harmful.*

Clinical ***angioedema*** *associated with* ***ARBs*** *have been reported.*

ACEIs and ARBs can provoke ***hyperkalemia*** *in the setting of CKD or diabetes with type 4 renal tubular acidosis.*

In patients with stage 3 CKD with proteinuria, initiation of ACEI or ARB therapy is often associated with a small transient increase in serum creatinine; therapy can be continued unless the elevation in creatinine is ***greater than 30%,*** *an indication to decrease the dose or temporarily withhold therapy.*

ACEIs and ARB*s have been used together for extra renal protection in proteinuric patients.*

ACEIs are easy to use and have a rather flat dose-response curve.

In ALLHAT, ACEI monotherapy with lisinopril was equivalent to amlodipine or chlorthalidone monotherapy in all aspects except for producing a smaller reduction in BP and thus less stroke protection in black hypertensive individuals.

*As monotherapy, **ACEIs are generally less effective** in lowering BP in **black patients and in older patients with low-renin hypertension,** when combined with a low-dose diuretic or CCB they are quite effective in these groups .*

*ACEIs have been shown to be **equivalent to CCBs in protecting against coronary events***

Slightly less effective in protecting against stroke, but better in protecting against heart failure.

ARBs may confer the same benefits as ACEIs in treating hypertension while avoiding the ACEI-related cough .

ACEIs and ARBs have become standard first-line antihypertensive

ACEIs and ARBs have comparable effects on renal function.

ACEIs and ARBs may prevent or slow progression from glucose intolerance to type 2 diabetes

ARBs produce more regression of left ventricular hypertrophy (LVH) than do other antihypertensive drugs.

Side Effects

All RAS inhibitors are ***contraindicated in pregnancy (cause fetal renal agenesis and other birth defects.***

The most common side effect of ACEIs is ***a dry cough****, which is more common in black patients and more common still in Asian patients.*

If a cough develops in a patient taking an ACEI who needs RAS blockade, an ARB should be substituted.

Choice of antihypertensive agents

ACEi and ARB's are the preffered agents in the management of hypertensive CKD, both in diabetics and nondiabetic CKD patients. The superiority of ACEi & ARB's in the management of hypertensive CKD and slowing the rate of progression of CKD is greater in pts with higher levels of proteinuria.

[Maschio G,et al NEJM 1996]

REIN study failed to show a therapeutic advantage of ramipril in nondiabetic CKD pts with proteinuria of<3g/24h,in slowing the progression .

ALLHAT study included 33,357 individuals, 5662 pts with CKD with eGFR <60 ml/min.

The follow-up period was over 4.9years.

Lisinopril was not more effective than chlorothalidone in slowing the progression of CHD, CKD .

Consequently, the therapeutic advantage of ACEi, or ARB's is uncertain, particularly in early CKD and in those with nondiabetic nephropathy and proteinuria of <1g/24h.

[Levey AS,et al Ann Inern Med 2006]

The UKPDS study confirmed that lower BP led to slower decline in renal function regardless of whether
Atenolol or captopril was used.

[UKPDS. BMJ 1998]

The indiscriminate use of ACEi & ARB's is not without risks. Patients with renovascular disease and ischemic nephropathy may be at risk of further deterioration of renal function when using these agents.

It is generally accepted that an up to 30% ↑ within a week, or a fall in GFR of <25% is acceptable, and predictable upon initiation of ACEi & ARB's in pts with CKD .

- *Studies have shown ACE-I to be of superior benefit in reducing the development of micro- & macroalbuminuria in pts with T1 DM including normotensivs.*

[lancet 2000]

Until recently, there have been little data from large prospective trials regarding the effectiveness of ACE-I for T2 diabetic nephropathy. In the Micro-Hope study of 3577 primarily T2 diabetic subjects Ramipril showed significant benefit over placebo in preventing The progression from microalbuminuric to overt nephropathy[24% RR] , and a nonsignificant↓in new microalbuminuria.

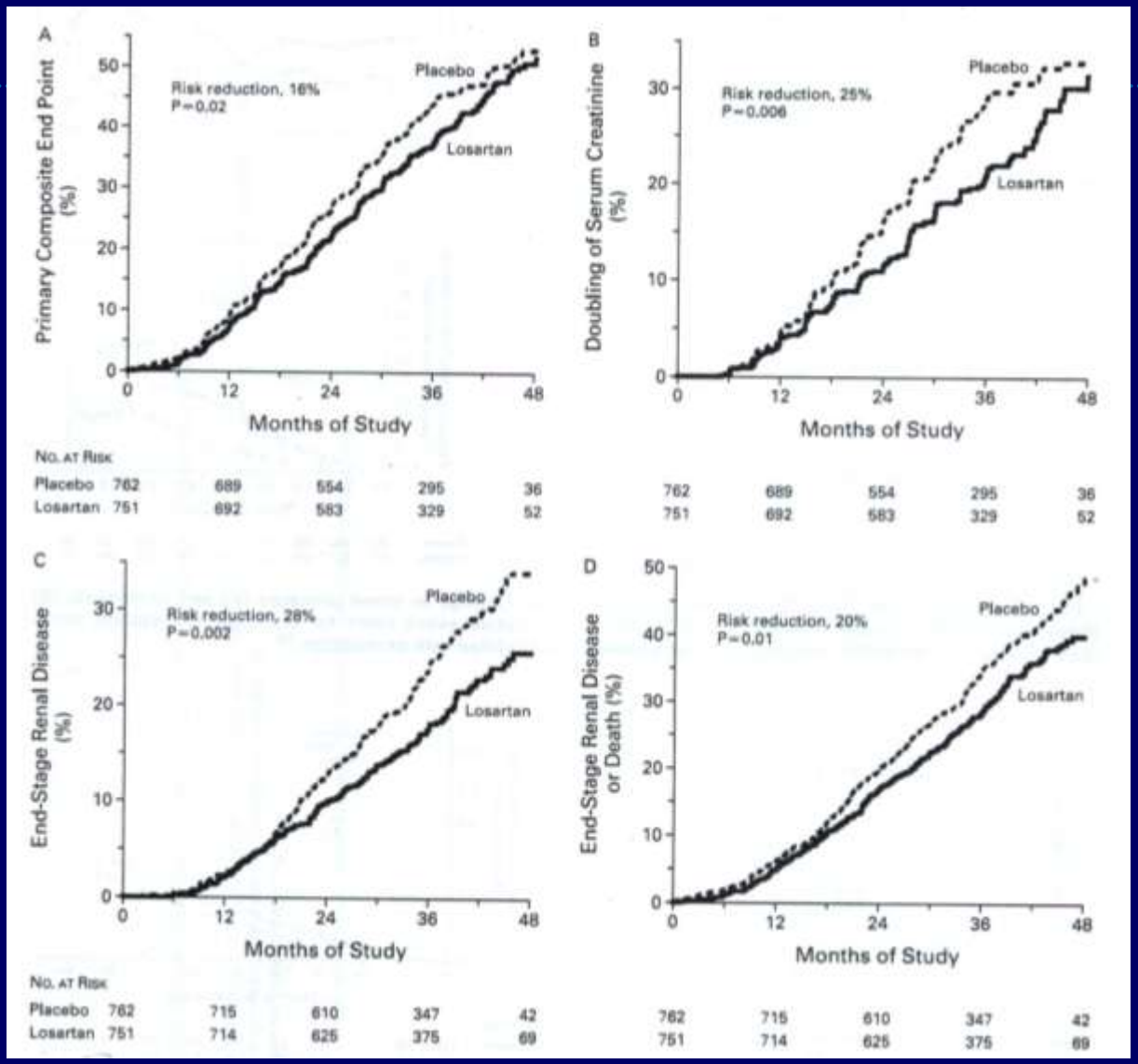
[Lancet 2000]

For ARBs, more evidence of benefit in prevention and progression of nephropathy exists for T2 than T1 diabetes.

In RENNAL study, 1513 hypertensive pts with T2 diabetes who had overt proteinuria, s.creat 1.3-3mg/dl

Patients were randomized to losartan or placebo. The BP was controlled < 140/90 in both groups.

Losartan produced RRR of 16% in comparison with placebo, in the composite endpoints of a doubling of s. creat., ESRD, or death.


A
Primary Composite End Point (%)
Risk reduction, 16%
P=0.02
Placebo
Losartan
Months of Study
No. at Risk
Placebo 762 689 554 295 36
Losartan 751 692 583 329 52
B
Doubling of Serum Creatinine (%)
Risk reduction, 25%
P=0.006
Placebo
Losartan
Months of Study
762 689 554 295 36
751 692 583 329 52
C
End-Stage Renal Disease (%)
Risk reduction, 28%
P=0.002
Placebo
Losartan
Months of Study
No. at Risk
Placebo 762 715 610 347 42
Losartan 751 714 625 375 69
D
End-Stage Renal Disease or Death (%)
Risk reduction, 20%
P=0.01
Placebo
Losartan
Months of Study
762 715 610 347 42
751 714 625 375 69

- *Interestingly, subanalysis from RENNAL study, demonstrated that the degree of reduction of proteinuria in the first 6 months, correlated +ve with reduction In renal events and ESRD. A similar reduction was found for CV endpoints.*

[De zeeuw D,et al AJH 2004]

ACE-I or ARB does it matter ?

This question was addressed in the DETAIL study. In this long term [5 ys],study in a double blind Study in a mixed population of micro- and macroalbuminuric pts with T2DM, the effects of An ACE-I Enalapril was compared with An ARB telmisartan .

The main endpoint was fall in GFR. After 5 ys the fall from baseline was similar in the 2 groups (15 ml/min in the ACE-I vs. 17ml/min in the ARB group).

BP reduction was similar in the 2 groups, and no cases of ESRD and only very few CV events were observed.
[Parving HH et al NEJM 2005]